



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 45/06</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 96/41645</b> <b>(43) International Publication Date:</b> 27 December 1996 (27.12.96)
<b>(21) International Application Number:</b> PCT/US96/09905 <b>(22) International Filing Date:</b> 11 June 1996 (11.06.96) <b>(30) Priority Data:</b> 08/489,415                      12 June 1995 (12.06.95)                      US <b>(71) Applicant:</b> G.D. SEARLE & CO. [US/US]; Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US). <b>(72) Inventors:</b> ISAKSON, Peter, C.; 2292 Ridgley Woods Drive, Clarkson Valley, MO 63005 (US). ANDERSON, Gary, D.; 1886 Woodhollow Drive #203, Maryland Heights, MO 63043 (US). GREGORY, Susan, A.; 4400 Lindell Boulevard #20A, St. Louis, MO 63108 (US). <b>(74) Agents:</b> BULLOCK, Joseph, W. et al.; G.D. Searle & Co., Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> COMBINATION OF A CYCLOOXYGENASE-2 INHIBITOR AND A LEUKOTRIENE B <sub>4</sub> RECEPTOR ANTAGONIST FOR THE TREATMENT OF INFLAMMATIONS  <b>(57) Abstract</b>  Combinations of a cyclooxygenase-2 inhibitor and a leukotriene B <sub>4</sub> receptor antagonist are described for treatment of inflammation and inflammation-related disorders.		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

COMBINATION OF A CYCLOOXYGENASE-2 INHIBITOR AND A LEUKOTRIENE B<sub>4</sub> RECEPTOR  
ANTAGONIST FOR THE TREATMENT OF INFLAMMATIONS

5

FIELD OF THE INVENTION

This invention is in the field of  
antiinflammatory pharmaceutical agents and  
10 specifically relates to co-administration of an  
inhibitor of cyclooxygenase-2 and a leukotriene B<sub>4</sub>  
receptor antagonist for treating inflammation and  
inflammation-related disorders, such as arthritis.

15

BACKGROUND OF THE INVENTION

Prostaglandins play a major role in the  
inflammation process, and the inhibition of  
prostaglandin production, especially production of  
20 PGG<sub>2</sub>, PGH<sub>2</sub> and PGE<sub>2</sub>, has been a common target of  
antiinflammatory drug discovery. However, common non-  
steroidal antiinflammatory drugs (NSAIDs) that are  
active in reducing the prostaglandin-induced pain and  
swelling associated with the inflammation process are  
25 also active in affecting other prostaglandin-regulated  
processes not associated with the inflammation  
process. Thus, use of high doses of most common  
NSAIDs can produce severe side effects, including life  
threatening ulcers, that limit their therapeutic  
30 potential. An alternative to NSAIDs is the use of  
corticosteroids, which have even more drastic side  
effects, especially when long term therapy is  
involved.

Previous NSAIDs have been found to prevent the  
35 production of prostaglandins by inhibiting enzymes in  
the human arachidonic acid/prostaglandin pathway  
including the enzyme cyclooxygenase (COX). The recent

discovery of an inducible enzyme associated with inflammation (named "cyclooxygenase-2 (COX-2)" or "prostaglandin G/H synthase II") provides a viable target of inhibition which more effectively reduces inflammation and produces fewer and less drastic side effects.

In another portion of the arachidonic acid pathway, physiologically active leukotrienes, such as leukotriene B<sub>4</sub> (LTB<sub>4</sub>), leukotriene C<sub>4</sub> (LTC<sub>4</sub>) and leukotriene D<sub>4</sub> (LTD<sub>4</sub>) and other metabolites, are produced by the 5-lipoxygenase-mediated (5-LO) oxidation of arachidonic acid. These leukotrienes have been implicated in various inflammation-related disorders and allergic diseases, and thus compounds which inhibit leukotriene A<sub>4</sub> conversion to leukotriene B<sub>4</sub>, such as compounds which inhibit leukotriene A<sub>4</sub> hydrolase are useful in the treatment of disease states in which leukotrienes play an important role.

It is believed that selective inhibitors of cyclooxygenase-2 and of leukotriene A<sub>4</sub> hydrolase, which affect the two enzymes at low concentrations, will decrease the incidence and severity more completely. These compositions also will beneficially affect the damage caused by the various inflammatory diseases and inflammation-related disorders mediated by cyclooxygenase-2 and leukotriene A<sub>4</sub> hydrolase. These compositions also will not have the level of gastrointestinal side effects commonly associated with traditional NSAIDs.

Compounds which selectively inhibit cyclooxygenase-2 have been described in U.S. patents 5,380,738, 5,344,991, 5,393,790, 5,466,823, 5,434,178, 5,474,995, 5,510,368 and WO documents WO96/06840, WO96/03388, WO96/03387, WO95/15316, WO94/15932, WO94/27980, WO95/00501, WO94/13635, WO94/20480, and WO94/26731.

Compounds which affect leukotriene B<sub>4</sub> have been described. U.S. Patent No. 5,384,318 describes substituted sulfonamides for the treatment of asthma. U.S. patent No. 5,246,965 describes aryl ethers as leukotriene B<sub>4</sub> receptor antagonists.

Combined therapies of NSAIDs and other reagents are known in the art. Brooks and Karl describe the treatment of hay fever with combined antihistamines and a cyclooxygenase-inhibiting drug (flurbiprofen) (J. Allergy Clin. Immunol., **81**, 110 (1988)). J. Basmajian (Spine, **14**, 438 (1989)) describes the combination of the analgesic diflunisal and an antispasm agent in the treatment of back pain. V. Fossaluzza and S. DeVita describe the combined therapy of ibuprofen and an antispasm agent to reduce morning stiffness associated with primary fibromyalgia syndrome (Int. J. Clin. Pharm. Res., **XII**, 99 (1992)). R. Greenwald et al. (J. Rheumatol., **19**, 927 (1992)) report the combination of tetracycline and the NSAID flurbiprofen ameliorates the tissue damage associated with rheumatoid arthritis.

Combination analgesics have been reported (W. Beaver, Am. J. Med., **77**, 38 (1984)) although such combinations do not substantially reduce adverse effects.

The combination of NSAIDs and steroids have been described. A combination of indomethacin, steroid and lipopolysaccharide has been reported for the treatment of spinal injury (L. Guth et al., Proc. Natl. Acad. Sci. USA, **91**, 12308 (1994)). G. Hughes et al. describe combinations of corticosteroids with NSAIDs for the treatment of sunburn (Dermatology, **184**, 54 (1992)). C. Stewart et al. (Clin. Pharmacol. Ther., **47**, 540 (1990)) describe the combination of naproxen and methotrexate as safe, although concurrent administrations of methotrexate with other NSAIDs have been reported to be toxic and sometimes fatal. A

combination of a dual 5-lipoxygenase/cyclooxygenase inhibitor with a glucocorticoid is described for the treatment of skin disorders (K. Tramposch, Inflammation, **17**, 531 (1993)). Combinations of NSAIDs and steroids should be used in the treatment of scleritis only if patients are not responsive to any other treatment (S. Lightman and P. Watson, Am. J. Ophthalmol., **108**, 95 (1989)).

Combinations of cyclooxygenase inhibitors, lipoxygenase inhibitors, collagenase inhibitors and cytotoxic agents have been used in the treatment of non-small-cell lung cancers (B. Teicher *et al.*, Cancer. Chemother. Pharmacol., **33**, 515 (1994)).

Combinations of naproxen with other NSAIDs have been described in the treatment of arthritis. R. Willikens and E. Segre (Arthritis Rheum., **19**, 677 (1976)) describe the combination of aspirin and naproxen as being more effective than aspirin alone for the treatment of rheumatoid arthritis. Naproxen and acetaminophen together were described for treating the pain associated with arthritis (P. Seideman *et al.*, Acta Orthop. Scand., **64**, 285 (1993)). However, combinations of naproxen with indomethacin or ibuprofen offer no advantage in the treatment of arthritis [M. Seifert and C. Engler (Curr. Med. Res. Opin., **7**, 38 (1980))]. European patent document EP485,111, published May 13, 1992, describes the synergistic combination of lipoxygenase inhibitors and NSAID's for the treatment of inflammatory disease.

There have been no reported combinations of a cyclooxygenase-2 selective inhibitor and a leukotriene B<sub>4</sub> receptor antagonist.

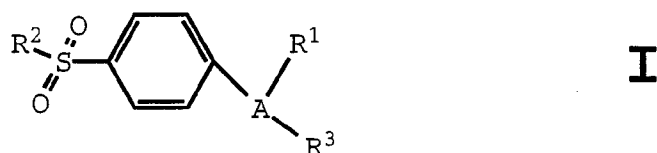
#### DESCRIPTION OF THE INVENTION

35

The invention involves a method of treating a subject having inflammation or an inflammation-related

disorder with a combination comprising a therapeutically-effective amount of a cyclooxygenase-2 inhibitor and a leukotriene B<sub>4</sub> receptor antagonist.

5 In addition, the invention describes a combination comprising a therapeutically-effective amount of a leukotriene B<sub>4</sub> receptor antagonist and a cyclooxygenase-2 inhibitor selected from Taisho NS-398, meloxicam, floculide, Merck MK-966, Merck L-752,860 and compounds of Formula I



wherein A is a substituent selected from partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

wherein R<sup>1</sup> is at least one substituent selected from heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R<sup>1</sup> is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

wherein R<sup>2</sup> is methyl or amino; and

wherein R<sup>3</sup> is a radical selected from hydrido, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclioxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl,

alkoxycarbonylalkyl, aminocarbonyl,  
aminocarbonylalkyl, alkylaminocarbonyl, N-  
arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl,  
alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-  
5 arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-  
alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-  
arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-  
aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy,  
aralkoxy, arylthio, aralkylthio, alkylsulfinyl,  
10 alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-  
arylaminosulfonyl, arylsulfonyl, N-alkyl-N-  
arylaminosulfonyl; or a pharmaceutically-acceptable  
salt thereof.

Combinations of the invention would be useful  
15 for, but not limited to, the treatment of inflammation  
in a subject, and for treatment of other inflammation-  
associated disorders, such as, as an analgesic in the  
treatment of pain and headaches, or as an antipyretic  
for the treatment of fever. For example, combinations  
20 of the invention would be useful to treat arthritis,  
including but not limited to rheumatoid arthritis,  
spondyloarthropathies, gouty arthritis, osteoarthritis,  
systemic lupus erythematosus and juvenile arthritis.  
Such combinations of the invention would be useful in  
25 the treatment of asthma, bronchitis, menstrual cramps,  
tendinitis, bursitis, and skin related conditions such  
as psoriasis, eczema, burns and dermatitis.

Combinations of the invention also would be useful to  
treat gastrointestinal conditions such as inflammatory  
30 bowel disease, Crohn's disease, gastritis, irritable  
bowel syndrome and ulcerative colitis and for the  
prevention or treatment of cancer, such as colorectal  
cancer. Combinations of the invention would be useful  
in treating inflammation in such diseases as vascular  
35 diseases, migraine headaches, periarteritis nodosa,  
thyroiditis, aplastic anemia, Hodgkin's disease,  
sclerodoma, rheumatic fever, type I diabetes,



myasthenia gravis, multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, hypersensitivity, swelling occurring after injury, myocardial ischemia, and the like. The compounds would also be useful in the treatment of ophthalmic diseases, such as retinitis, retinopathies, conjunctivitis, uveitis, ocular photophobia, and of acute injury to the eye tissue. The compounds would also be useful in the treatment of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis. The compounds would also be useful for the treatment of certain central nervous system disorders such as cortical dementias including Alzheimer's disease. The combinations of the invention are useful as anti-inflammatory agents, such as for the treatment of arthritis, with the additional benefit of having significantly less harmful side effects. As inhibitors of 5-lipoxygenase, these compositions would also be useful in the treatment of allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, atherosclerosis and central nervous system damage resulting from stroke, ischemia and trauma.

Besides being useful for human treatment, these compounds are also useful for treatment of mammals, including horses, dogs, cats, rats, mice, sheep, pigs, etc.

The term "cyclooxygenase-2 inhibitor" embraces compounds which selectively inhibit cyclooxygenase-2 over cyclooxygenase-1. Preferably, the compounds have a cyclooxygenase-2  $IC_{50}$  of less than about 0.5  $\mu M$ , and also have a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 50, and more preferably of at least 100. Even more preferably, the compounds have a cyclooxygenase-1  $IC_{50}$  of greater than about 1  $\mu M$ , and more preferably of greater than 20  $\mu M$ . Such preferred selectivity may

indicate an ability to reduce the incidence of common NSAID-induced side effects.

The term "leukotriene B<sub>4</sub> receptor antagonist" embraces compounds which selectively antagonize a leukotriene B<sub>4</sub> receptor with an IC<sub>50</sub> of less than about 10 μM. More preferably, the leukotriene B<sub>4</sub> receptor antagonists have an IC<sub>50</sub> of less than about 1 μM.

The phrase "combination therapy", "co-administration" or "co-therapy", in defining use of a cyclooxygenase-2 inhibitor agent and a leukotriene B<sub>4</sub> receptor antagonist agent, are intended to embrace administration of each agent in a sequential manner in a regimen that will provide beneficial effects of the drug combination, and is intended as well to embrace co-administration of these agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of these active agents or in multiple, separate capsules for each agent.

The phrase "therapeutically-effective" is intended to qualify the amount of each agent for use in the combination therapy which will achieve the goal of improvement in inflammation severity and the frequency of incidence over treatment of each agent by itself, while avoiding adverse side effects typically associated with alternative therapies.

Preferred leukotriene B<sub>4</sub> receptor antagonists include Bayer Bay-x-1005, Ciba-Geigy CGS-25019C, ebselen, Leo Denmark ETH-615, Lilly LY-293111, Ono ONO-4057, Terumo TMK-688, Boehringer Ingelheim BI-RM-270, Lilly LY 213024, Lilly LY 264086, Lilly LY 292728, Ono ONO LB457, Pfizer 105696, Perdue Frederick PF 10042, Rhone-Poulenc Rorer RP 66153, SmithKline Beecham SB-201146, SmithKline Beecham SB-201993, Searle SC-53228, Sumitamo SM 15178, American Home Products WAY 121006, Bayer Bay-o-8276, calcitriol, Warner-Lambert CI-987, Merck and Co. L-651392, Lilly LY 210073, Lilly LY 223982, Lilly LY 233569, Lilly LY-

255283, Merck and Co. MK-591, Merck and CO. MK-886, Ono ONO-LB-448, Purdue Frederick PF-5901, Rhone-Poulenc Rorer RG 14893, Rhone-Poulenc Rorer RP 66364, Rhone-Poulenc Rorer RP 69698, Searle SC-41930, Searle SC-50505, Searle SC-51146, SmithKline Beecham SK&F-104493, and Teijin TEI-1338.

More preferred leukotriene B<sub>4</sub> receptor antagonists include Bayer Bay-x-1005, Ciba-Geigy CGS-25019C, ebselen, Leo Denmark ETH-615, Lilly LY-293111, Ono ONO-4057, Terumo TMK-688, Boehringer Ingleheim BI-RM-270, Lilly LY 213024, Lilly LY 264086, Lilly LY 292728, Ono ONO LB457, Pfizer 105696, Purdue Frederick PF 10042, Rhone-Poulenc Rorer RP 66153, SmithKline Beecham SB-201146, SmithKline Beecham SB-201993, Searle SC-53228, Sumitamo SM 15178, and American Home Products WAY 121006.

Even more preferred leukotriene B<sub>4</sub> receptor antagonists include Bayer Bay-x-1005, Ciba-Geigy CGS-25019C, ebselen, Leo Denmark ETH-615, Lilly LY-293111, Ono ONO-4057, and Terumo TMK-688.

A preferred class of compounds which inhibit cyclooxygenase-2 consists of compounds of Formula I wherein A is selected from 5- or 6-member partially unsaturated heterocyclyl, 5- or 6-member unsaturated heterocyclyl, 9- or 10-member unsaturated condensed heterocyclyl, lower cycloalkenyl and phenyl; wherein R<sup>1</sup> is selected from 5- and 6-membered heterocyclyl, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R<sup>1</sup> is optionally substituted at a substitutable position with one or more radicals selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxy carbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylamino, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio; wherein R<sup>2</sup> is methyl or amino; and wherein R<sup>3</sup> is a radical selected from

hydrido, oxo, cyano, carboxyl, lower alkoxy carbonyl, lower carboxyalkyl, lower cyanoalkyl, halo, lower alkyl, lower alkyloxy, lower cycloalkyl, phenyl, lower haloalkyl, 5- or 6-membered heterocyclyl, lower hydroxylalkyl, lower aralkyl, acyl, phenylcarbonyl, lower alkoxyalkyl, 5- or 6-membered heteroaryloxy, aminocarbonyl, lower alkylaminocarbonyl, lower alkylamino, lower aminoalkyl, lower alkylaminoalkyl, phenyloxy, and lower aralkoxy; or a pharmaceutically-acceptable salt thereof.

A more preferred class of compounds which inhibit cyclooxygenase-2 consists of compounds of Formula I wherein A is selected from oxazolyl, isoxazolyl, thienyl, dihydrofuryl, furyl, pyrrolyl, pyrazolyl, thiazolyl, imidazolyl, isothiazolyl, benzofuryl, cyclopentenyl, cyclopentadienyl, phenyl, and pyridyl; wherein R<sup>1</sup> is selected from pyridyl optionally substituted at a substitutable position with one or more methyl radicals, and phenyl optionally substituted at a substitutable position with one or more radicals selected from methyl, ethyl, isopropyl, butyl, *tert*-butyl, isobutyl, pentyl, hexyl, cyano, fluoromethyl, difluoromethyl, trifluoromethyl, carboxyl, methoxycarbonyl, ethoxycarbonyl, hydroxymethyl, trifluoromethoxy, hydroxyl, amino, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-dipropylamino, N-butylamino, N-methyl-N-ethylamino, phenylamino, methoxymethyl, methylsulfinyl, fluoro, chloro, bromo, methoxy, ethoxy, propoxy, *n*-butoxy, pentoxy, and methylthio; wherein R<sup>2</sup> is methyl or amino; and wherein R<sup>3</sup> is a radical selected from hydrido, oxo, cyano, carboxyl, methoxycarbonyl, ethoxycarbonyl, carboxypropyl, carboxymethyl, carboxyethyl, cyanomethyl, fluoro, chloro, bromo, methyl, ethyl, isopropyl, butyl, *tert*-butyl, isobutyl, pentyl, hexyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, heptafluoropropyl, difluoroethyl, difluoropropyl,

methoxy, ethoxy, propoxy, n-butoxy, pentoxy, cyclohexyl, phenyl, pyridyl, thienyl, thiazolyl, oxazolyl, furyl, pyrazinyl, hydroxymethyl, hydroxylpropyl, benzyl, formyl, phenylcarbonyl, methoxymethyl, furylmethyloxy, aminocarbonyl, N-methylaminocarbonyl, N,N-dimethylaminocarbonyl, N,N-dimethylamino, N-ethylamino, N,N-dipropylamino, N-butylamino, N-methyl-N-ethylamino, aminomethyl, N,N-dimethylaminomethyl, N-methyl-N-ethylaminomethyl, benzyloxy, and phenyloxy; or a pharmaceutically-acceptable salt thereof.

A family of specific compounds of particular interest within Formula I consists of compounds and pharmaceutically-acceptable salts thereof as follows:

- 15 5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole;  
4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)pyrazole;  
4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide  
20 4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;  
4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide;  
25 4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;  
4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;  
4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl)benzenesulfonamide;  
30 4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-yl)benzenesulfonamide;  
4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-yl)benzenesulfonamide  
35 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

- 4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 5 4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 10 4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 15 4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;
- 4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 20 4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 25 4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;
- 4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 30 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
- 4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
- 35 6-(4-fluorophenyl)-7-[4-(methylsulfonyl)phenyl]spiro[3.4]oct-6-ene;

- 5-(3-chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;  
4-[6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
- 5 5-(3,5-dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;  
5-(3-chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;  
4-[6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
- 10 2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;  
2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;
- 15 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole;  
4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;  
4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole;
- 20 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole;  
4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole;
- 25 2-[(3,5-dichlorophenoxy)methyl]-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]thiazole;  
5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;  
1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene;
- 30 4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl]benzenesulfonamide;  
5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hepta-4,6-diene;
- 35 4-[6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-yl]benzenesulfonamide;

- 6-(4-fluorophenyl)-2-methoxy-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;  
2-bromo-6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;  
5 6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyl-pyridine-3-carbonitrile;  
4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;  
4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;  
10 4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;  
3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;  
15 2-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;  
2-methyl-4-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;  
2-methyl-6-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;  
20 4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;  
2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;  
25 4-[2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;  
2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-methyl-1H-imidazole;  
2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-1H-imidazole;  
30 2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;  
2-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;  
35 1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole;



- 2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
- 4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 5 2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
- 4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 10 2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
- 4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- 1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole;
- 15 4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- 20 4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- 1-allyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;
- 25 4-[1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl]benzenesulfonamide;
- N-phenyl-[4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;
- 30 ethyl [4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetate;
- 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-1H-pyrazole;
- 35 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole;

- 1-ethyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;
- 5- (4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethyl-1H-imidazole;
- 4-[4-(methylsulfonyl)phenyl]-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole;
- 5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;
- 10 2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;
- 5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-(2-propynyloxy)-6-(trifluoromethyl)pyridine;
- 2-bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;
- 15 4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide;
- 1-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene;
- 20 5-difluoromethyl-4-(4-methylsulfonylphenyl)-3-phenylisoxazole;
- 4-[3-ethyl-5-phenylisoxazol-4-yl]benzenesulfonamide;
- 4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- 25 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide;
- 1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- 30 1-[2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- 1-[2-(4-chlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- 1-[2-(2,4-dichlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- 35 1-[2-(4-trifluoromethylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

- 1-[2-(4-methylthiophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;  
1-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;  
5 4-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;  
1-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;  
4-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;  
10 4-[2-(4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;  
4-[2-(4-chlorophenyl)cyclopenten-1-yl]benzenesulfonamide;  
15 1-[2-(4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;  
1-[2-(2,3-difluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;  
4-[2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-yl]benzenesulfonamide;  
20 1-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;  
4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;  
25 4-[2-(2-methylpyridin-5-yl)cyclopenten-1-yl]benzenesulfonamide;  
ethyl 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]-2-benzyl-acetate;  
2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]acetic acid;  
30 2-(tert-butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole;  
4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole;  
35 4-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole; and

4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide.

The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene (-CH<sub>2</sub>-) radical. Where used, either alone or within other terms such as "haloalkyl", "alkylsulfonyl", "alkoxyalkyl" and "hydroxyalkyl", the term "alkyl" embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl and the like. The term "alkenyl" embraces linear or branched radicals having at least one carbon-carbon double bond of two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkyl radicals are "lower alkenyl" radicals having two to about six carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, allyl, propenyl, butenyl and 4-methylbutenyl. The term "alkynyl" denotes linear or branched radicals having two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkynyl radicals are "lower alkynyl" radicals having two to about ten carbon atoms. Most preferred are lower alkynyl radicals having two to about six carbon atoms. Examples of such radicals include propargyl, butynyl, and the like. The terms "alkenyl", "lower alkenyl", embrace radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations. The term "cycloalkyl" embraces saturated carbocyclic radicals

having three to twelve carbon atoms. More preferred cycloalkyl radicals are "lower cycloalkyl" radicals having three to about eight carbon atoms. Examples of such radicals include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The term "cycloalkenyl" embraces partially unsaturated carbocyclic radicals having three to twelve carbon atoms. More preferred cycloalkenyl radicals are "lower cycloalkenyl" radicals having four to about eight carbon atoms. Examples of such radicals include cyclobutenyl, cyclopentenyl, cyclopentadienyl and cyclohexenyl. The term "halo" means halogens such as fluorine, chlorine, bromine or iodine. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" embraces radicals having 1-6 carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl. The terms "alkoxy" and

"alkyloxy" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and *tert*-butoxy. The term "alkoxyalkyl" embraces alkyl radicals having one or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. The "alkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkoxy radicals. More preferred haloalkoxy radicals are "lower haloalkoxy" radicals having one to six carbon atoms and one or more halo radicals. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy. The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl. Aryl moieties may also be substituted at a substitutable position with one or more substituents selected independently from alkyl, alkoxyalkyl, alkylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkoxy, aralkoxy, hydroxyl, amino, halo, nitro, alkylamino, acyl, cyano, carboxy, aminocarbonyl, alkoxycarbonyl and aralkoxycarbonyl. The term "heterocyclo" embraces saturated, partially unsaturated and unsaturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Examples of saturated heterocyclo radicals include saturated 3 to 6-membered heteromonocyclic group containing 1 to 4 nitrogen atoms (e.g.

pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g. morpholinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., thiazolidinyl, etc.). Examples of partially unsaturated heterocyclo radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole. The term "heteroaryl" embraces unsaturated heterocyclo radicals. Examples of unsaturated heterocyclo radicals, also termed "heteroaryl" radicals include unsaturated 3 to 6 membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.) tetrazolyl (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.; unsaturated condensed heterocyclo group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyll, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl (e.g., tetrazolo[1,5-b]pyridazinyl, etc.), etc.; unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, furyl, etc.; unsaturated 3 to 6-membered heteromonocyclic group containing a sulfur atom, for example, thienyl, etc.; unsaturated 3- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.) etc.; unsaturated condensed heterocyclo group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g. benzoxazolyl, benzoxadiazolyl, etc.); unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms

and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl (e.g., 1,2,4- thiadiazolyl, 1,3,4- thiadiazolyl, 1,2,5-thiadiazolyl, etc.) etc.;

5   unsaturated condensed heterocyclo group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., benzothiazolyl, benzothiadiazolyl, etc.) and the like. The term also embraces radicals where heterocyclo radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran,

10   benzothiophene, and the like. Said "heterocyclo group" may have 1 to 3 substituents such as alkyl, hydroxyl, halo, alkoxy, oxo, amino and alkylamino. The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to about ten

15   carbon atoms attached to a divalent sulfur atom. More preferred alkylthio radicals are "lower alkylthio" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthio radicals are methylthio, ethylthio, propylthio, butylthio and

20   hexylthio. The term "alkylthioalkyl" embraces radicals containing an alkylthio radical attached through the divalent sulfur atom to an alkyl radical of one to about ten carbon atoms. More preferred alkylthioalkyl radicals are "lower alkylthioalkyl"

25   radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthioalkyl radicals include methylthiomethyl. The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to

30   a divalent  $-S(=O)-$  radical. More preferred alkylsulfinyl radicals are "lower alkylsulfinyl" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylsulfinyl radicals include methylsulfinyl, ethylsulfinyl, butylsulfinyl

35   and hexylsulfinyl. The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals  $-SO_2-$ .



"Alkylsulfonyl" embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. More preferred alkylsulfonyl radicals are "lower alkylsulfonyl" radicals having one to six carbon atoms. Examples of such lower alkylsulfonyl radicals include methylsulfonyl, ethylsulfonyl and propylsulfonyl. The "alkylsulfonyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkylsulfonyl radicals. The terms "sulfamyl", "aminosulfonyl" and "sulfonamidyl" denote  $\text{NH}_2\text{O}_2\text{S}-$ . The term "acyl" denotes a radical provided by the residue after removal of hydroxyl from an organic acid. Examples of such acyl radicals include alkanoyl and aroyl radicals. Examples of such lower alkanoyl radicals include formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, trifluoroacetyl. The term "carbonyl", whether used alone or with other terms, such as "alkoxycarbonyl", denotes  $-(\text{C}=\text{O})-$ . The term "aroyl" embraces aryl radicals with a carbonyl radical as defined above. Examples of aroyl include benzoyl, naphthoyl, and the like and the aryl in said aroyl may be additionally substituted. The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes  $-\text{CO}_2\text{H}$ . The term "carboxyalkyl" embraces alkyl radicals substituted with a carboxy radical. More preferred are "lower carboxyalkyl" which embrace lower alkyl radicals as defined above, and may be additionally substituted on the alkyl radical with halo. Examples of such lower carboxyalkyl radicals include carboxymethyl, carboxyethyl and carboxypropyl. The term "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl radical. More preferred are "lower alkoxycarbonyl" radicals with alkyl portions having 1

to 6 carbons. Examples of such lower alkoxycarbonyl (ester) radicals include substituted or unsubstituted methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and hexyloxycarbonyl. The terms

5 "alkylcarbonyl", "arylcarbonyl" and "aralkylcarbonyl" include radicals having alkyl, aryl and aralkyl radicals, as defined above, attached to a carbonyl radical. Examples of such radicals include substituted or unsubstituted methylcarbonyl,

10 ethylcarbonyl, phenylcarbonyl and benzylcarbonyl. The term "aralkyl" embraces aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenylethyl, and diphenylethyl. The aryl in said aralkyl may be additionally substituted

15 with halo, alkyl, alkoxy, haloalkyl and haloalkoxy. The terms benzyl and phenylmethyl are interchangeable. The term "heterocycloalkyl" embraces saturated and partially unsaturated heterocyclo-substituted alkyl radicals, such as pyrrolidinylmethyl, and heteroaryl-

20 substituted alkyl radicals, such as pyridylmethyl, quinolylmethyl, thienylmethyl, furylethyl, and quinolylethyl. The heteroaryl in said heteroaralkyl may be additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy. The term

25 "aralkoxy" embraces aralkyl radicals attached through an oxygen atom to other radicals. The term "aralkoxyalkyl" embraces aralkoxy radicals attached through an oxygen atom to an alkyl radical. The term "aralkylthio" embraces aralkyl radicals attached to a

30 sulfur atom. The term "aralkylthioalkyl" embraces aralkylthio radicals attached through a sulfur atom to an alkyl radical. The term "aminoalkyl" embraces alkyl radicals substituted with one or more amino radicals. More preferred are "lower aminoalkyl"

35 radicals. Examples of such radicals include aminomethyl, aminoethyl, and the like. The term "alkylamino" denotes amino groups which have been

substituted with one or two alkyl radicals. Preferred are "lower N-alkylamino" radicals having alkyl portions having 1 to 6 carbon atoms. Suitable lower alkylamino may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino or the like. The term "arylamino" denotes amino groups which have been substituted with one or two aryl radicals, such as N-phenylamino. The "arylamino" radicals may be further substituted on the aryl ring portion of the radical. The term "aralkylamino" embraces aralkyl radicals attached through an amino nitrogen atom to other radicals. The terms "N-arylaminoalkyl" and "N-aryl-N-alkyl-aminoalkyl" denote amino groups which have been substituted with one aryl radical or one aryl and one alkyl radical, respectively, and having the amino group attached to an alkyl radical. Examples of such radicals include N-phenylaminomethyl and N-phenyl-N-methylaminomethyl. The term "aminocarbonyl" denotes an amide group of the formula  $-C(=O)NH_2$ . The term "alkylaminocarbonyl" denotes an aminocarbonyl group which has been substituted with one or two alkyl radicals on the amino nitrogen atom. Preferred are "N-alkylaminocarbonyl" "N,N-dialkylaminocarbonyl" radicals. More preferred are "lower N-alkylaminocarbonyl" "lower N,N-dialkylaminocarbonyl" radicals with lower alkyl portions as defined above. The term "alkylaminoalkyl" embraces radicals having one or more alkyl radicals attached to an aminoalkyl radical. The term "aryloxyalkyl" embraces radicals having an aryl radical attached to an alkyl radical through a divalent oxygen atom. The term "arylthioalkyl" embraces radicals having an aryl radical attached to an alkyl radical through a divalent sulfur atom.

The present invention comprises a pharmaceutical composition comprising a therapeutically-effective

amount of a leukotriene B<sub>4</sub> receptor antagonist and of a cyclooxygenase-2 inhibitor compound in association with at least one pharmaceutically-acceptable carrier, adjuvant or diluent.

5       The present invention also comprises a method of treating inflammation or inflammation-associated disorders in a subject, the method comprising administering to the subject having or susceptible to such inflammation or disorder a therapeutically-  
10       effective amount of a leukotriene B<sub>4</sub> receptor antagonist and of a cyclooxygenase-2 inhibitor. The method of the present invention also includes prophylactic or chronic treatment, especially in the case of arthritis and other inflammatory conditions  
15       which can lead to deterioration in the joints.

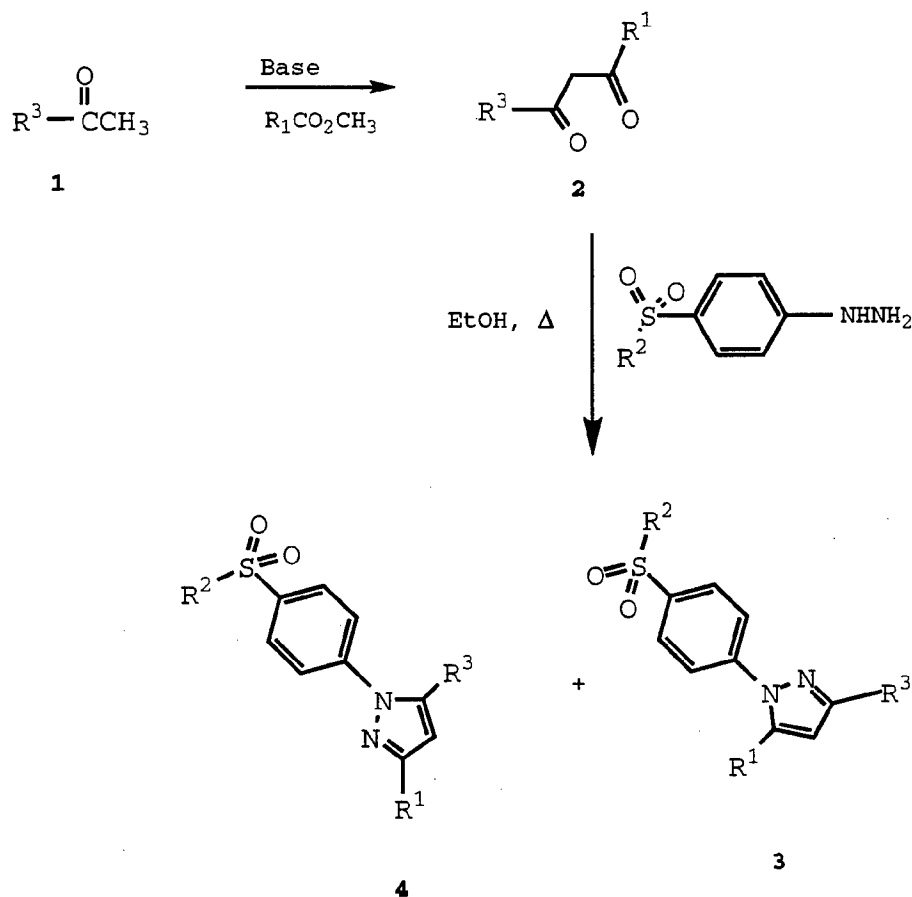
Also included in the family of compounds of Formula I are the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts  
20       and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of Formula I may be prepared from an  
25       inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic,  
30       heterocyclo, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, p-  
35       hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-

hydroxyethanesulfonic, sulfanilic, stearic, cyclohexylaminosulfonic, algenic,  $\beta$ -hydroxybutyric, salicylic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formula I include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound of Formula I by reacting, for example, the appropriate acid or base with the compound of Formula I.

#### GENERAL SYNTHETIC PROCEDURES

The cyclooxygenase-2 inhibitor compounds of the invention can be synthesized according to the following procedures of Schemes I-X, wherein the R<sup>1</sup>-R<sup>3</sup> substituents are as defined for Formula I, above, except where further noted.

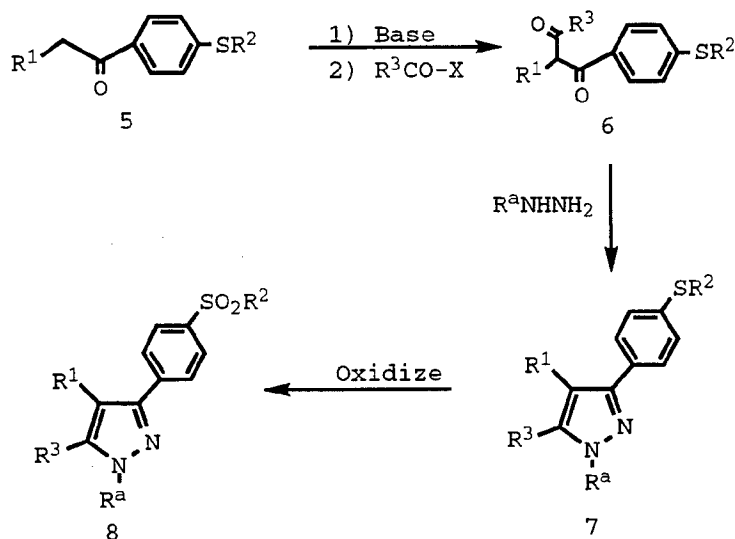
## Scheme I



Synthetic Scheme I shows the preparation of cyclooxygenase-2 inhibitor compounds, as described in U.S. patent No. 5,466,823, embraced by Formula I where R is Ar or Z (as defined in Scheme I), and R<sup>a</sup> is a radical defined above for the substituents optionally substituted on A. In step 1, ketone 1 is treated with a base, preferably NaOMe or NaH, and an ester, or ester equivalent, to form the intermediate diketone 2 (in the enol form) which is used without further purification. In step 2, diketone 2 in an anhydrous protic solvent, such as absolute ethanol or acetic acid, is treated with the hydrochloride salt or the free base of a substituted hydrazine at reflux to afford a mixture of pyrazoles 3 and 4.

Recrystallization or chromatography affords **3** usually as a solid. Similar pyrazoles can be prepared by methods described in U.S. Pat. Nos. 4,146,721, 5,051,518, 5,134,142 and 4,914,121.

## Scheme II

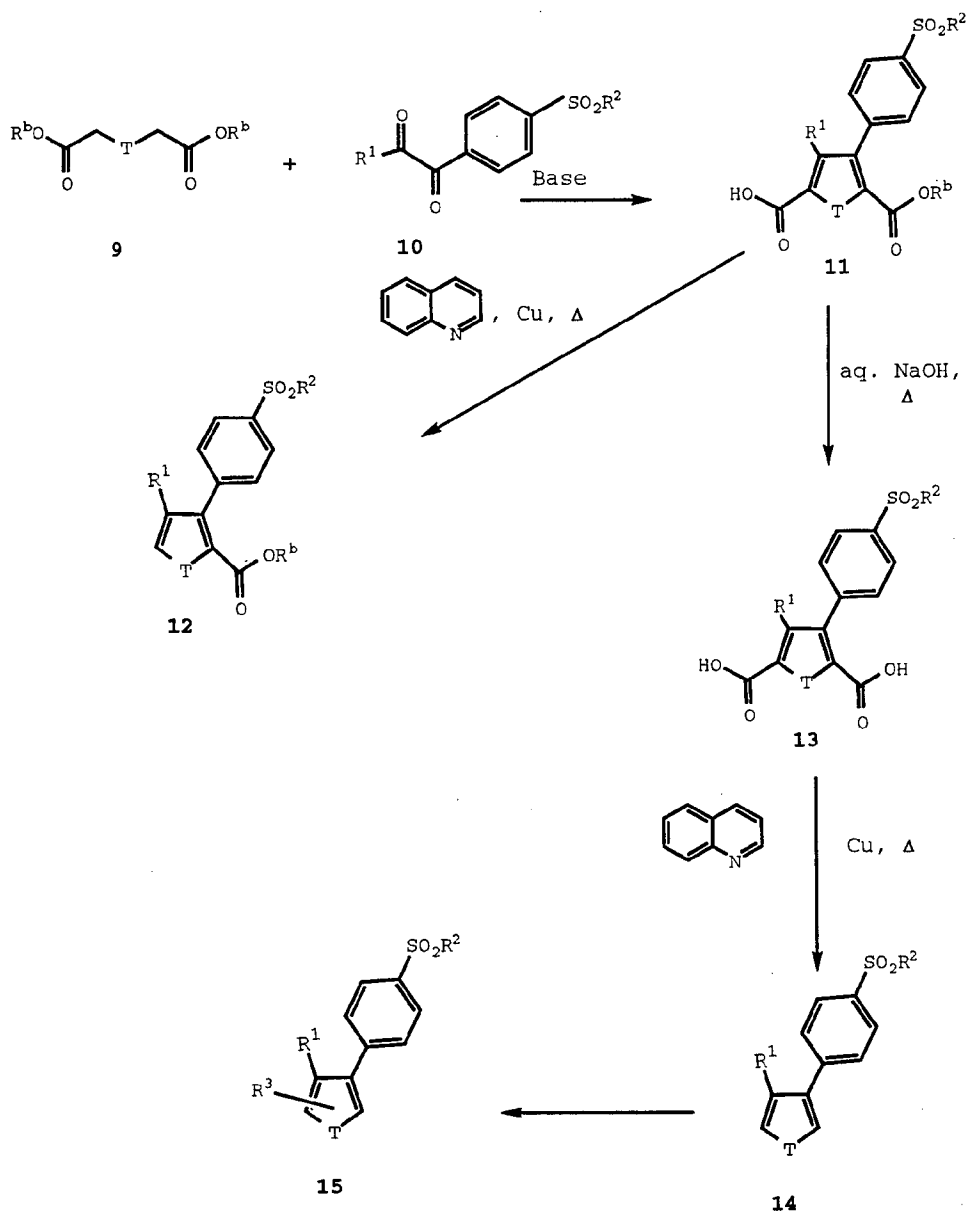


Scheme II shows the four step procedure for forming cyclooxygenase-2 inhibitor pyrazoles 8 as described in U.S. patent No. 5,486,534 (where R<sup>a</sup> is alkyl) from ketones 5. In step 1, ketone 5 is reacted with a base, such as lithium bis(trimethylsilyl)amide or lithium diisopropylamide (LDA) to form the anion. In step 2, the anion is reacted with an acetylating reagent to provide diketone 6. In step 3, the reaction of diketone 6 with hydrazine or a substituted hydrazine, gives pyrazole 7. In step 4, the pyrazole 7 is oxidized with an oxidizing reagent, such as Oxone<sup>®</sup> (potassium peroxymonosulfate), 3-chloroperbenzoic acid (MCPBA) or hydrogen peroxide, to give a mixture of the desired 3-(alkylsulfonyl)phenylpyrazole 8 and the 5-(alkylsulfonyl)phenylpyrazole isomer. The desired pyrazole 8, usually a white or pale yellow solid, is obtained in pure form either by chromatography or recrystallization.

Alternatively, diketone 6 can be formed from ketone 5 by treatment with a base, such as sodium hydride, in a solvent, such as dimethylformamide, and further reacting with a nitrile to form an  
5 aminoketone. Treatment of the aminoketone with acid forms the diketone 6. Similar pyrazoles can be prepared by methods described in U.S. Pat. No. 3,984,431.



## Scheme III

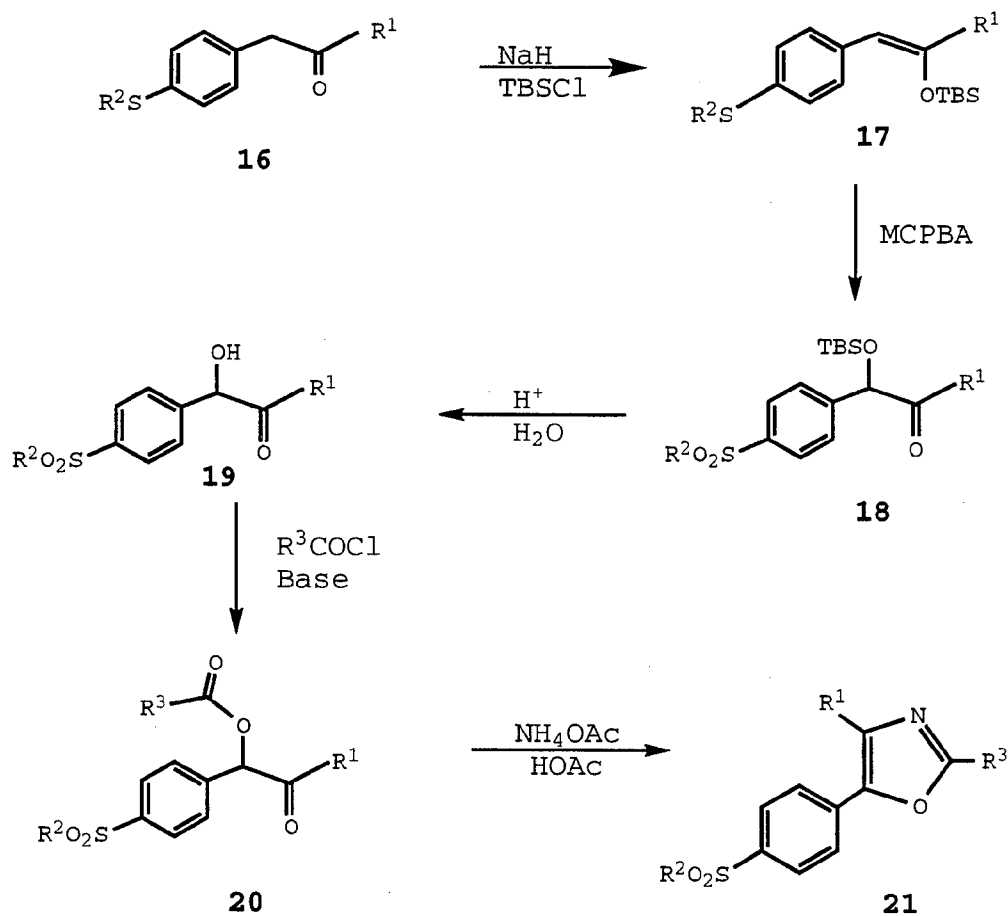


- 5 Cyclooxygenase-2 inhibitor diaryl/heteroaryl thiophenes (where T is S, and R<sup>b</sup> is alkyl) can be prepared by the methods described in U.S. Patent Nos. 4,427,693, 4,302,461, 4,381,311, 4,590,205, and 4,820,827, and PCT documents WO 95/00501 and
- 10 WO94/15932. Similar pyrroles (where T is N), furanones and furans (where T is O) can be prepared by

methods described in PCT documents WO 95/00501 and WO94/15932.

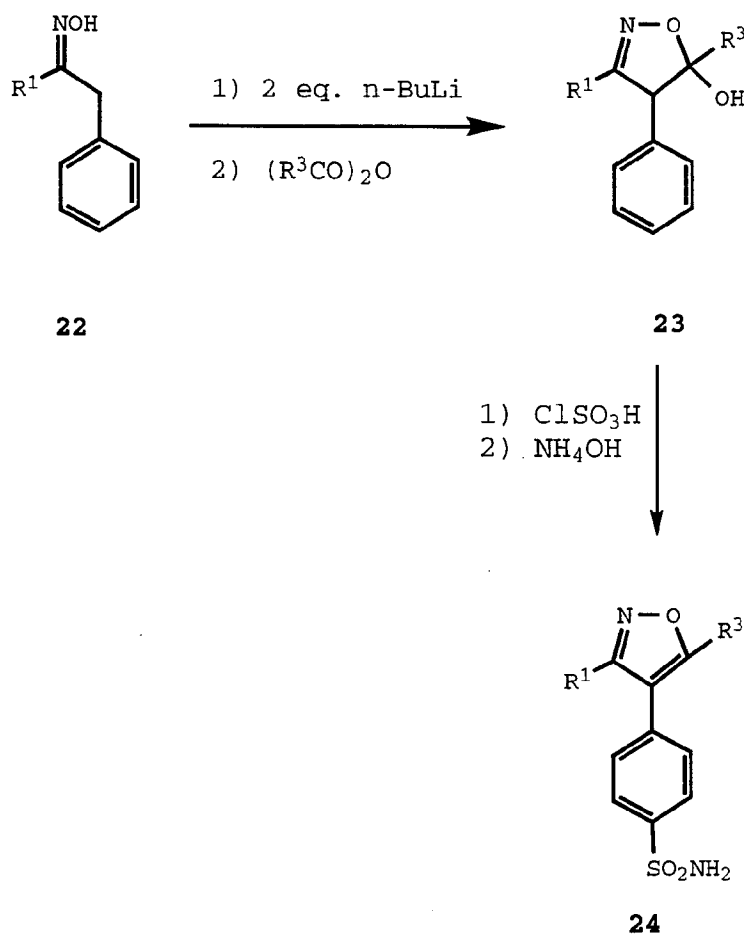
## Scheme IV

5



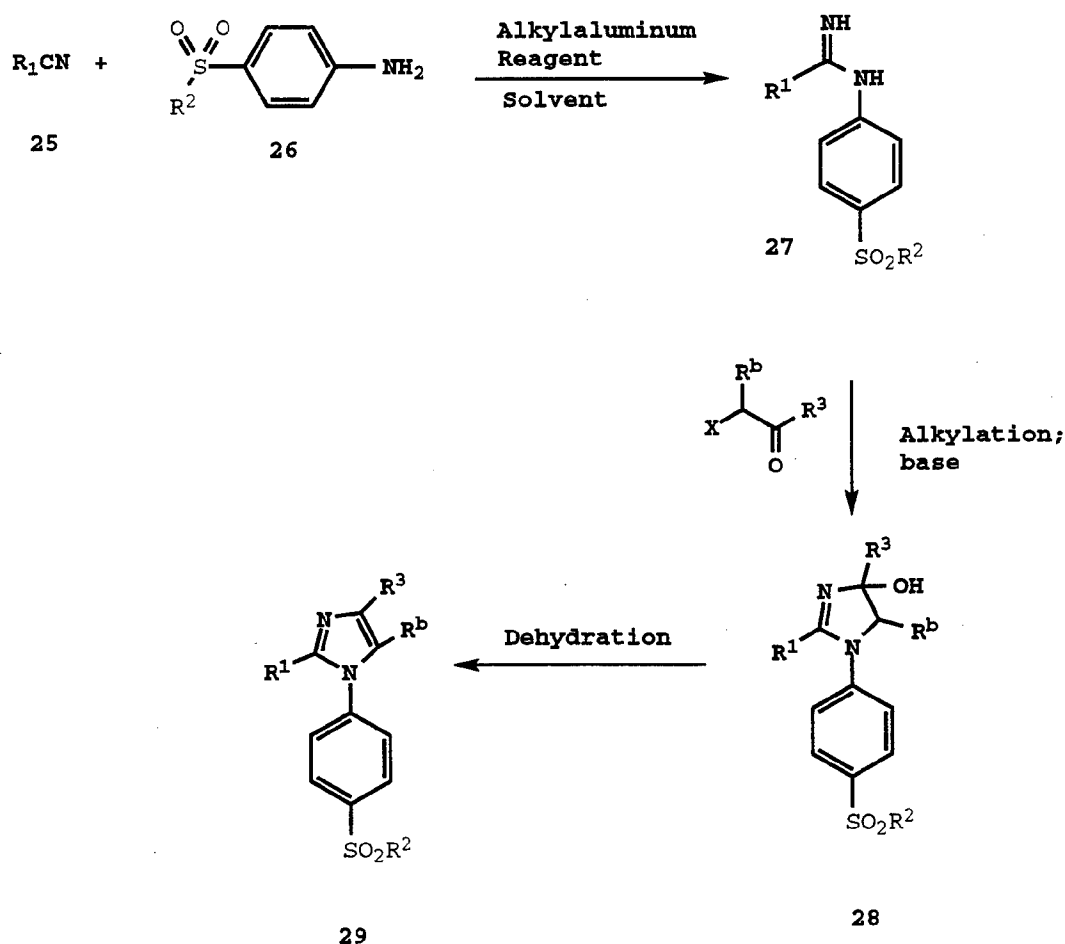
Cyclooxxygenase-2 inhibitor diaryl/heteroaryl oxazoles can be prepared by the methods described in U.S. Patent Nos. 3,743,656, 3,644,499 and 3,647,858, and PCT documents WO 95/00501 and WO94/27980.

## Scheme V



- 5           Cyclooxygenase-2 inhibitor diaryl/heteroaryl  
isoxazoles can be prepared by the methods described in  
United States application Serial No. 08/387,680, PCT  
documents WO92/05162, and WO92/19604, and European  
Publication EP 26928. Sulfonamides **24** can be formed  
10 from the hydrated isoxazole **23** in a two step  
procedure. First, hydrated isoxazole **23** is treated at  
about 0 °C with two or three equivalents of  
chlorosulfonic acid to form the corresponding sulfonyl  
chloride. In step two, the sulfonyl chloride thus  
15 formed is treated with concentrated ammonia to provide  
the sulfonamide derivative **24**.

## Scheme VI



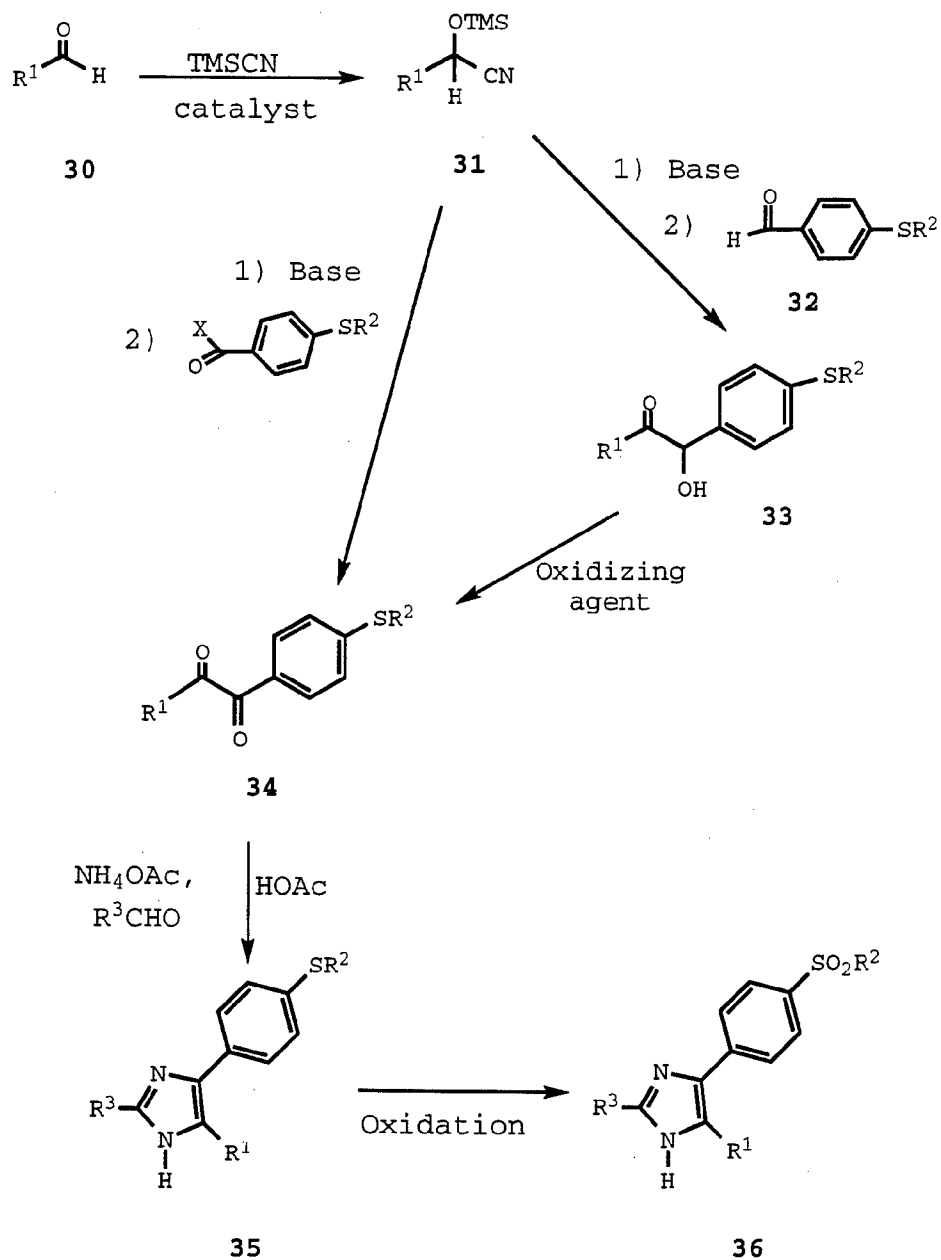
Scheme VI shows the three step preparation of the  
 5 cyclooxygenase-2 inhibitor imidazoles **29** of the  
 present invention. In step 1, the reaction of  
 substituted nitriles ( $\text{R}^1\text{CN}$ ) **25** with primary  
 phenylamines **26** in the presence of alkylaluminum  
 reagents such as trimethylaluminum, triethylaluminum,  
 10 dimethylaluminum chloride, diethylaluminum chloride in  
 the presence of inert solvents such as toluene,  
 benzene, and xylene, gives amidines **27**. In step 2,  
 the reaction of amidine **27** with 2-haloketones (where X  
 is Br or Cl) in the presence of bases, such as sodium  
 15 bicarbonate, potassium carbonate, sodium carbonate,  
 potassium bicarbonate or hindered tertiary amines such  
 as *N,N'*-diisopropylethylamine, gives the 4,5-

dihydroimidazoles **28** (where  $R^b$  is alkyl). Some of the suitable solvents for this reaction are isopropanol, acetone and dimethylformamide. The reaction may be carried out at temperatures of about 20°C to about 5 90°C. In step 3, the 4,5-dihydroimidazoles **28** may be dehydrated in the presence of an acid catalyst such as 4-toluenesulfonic acid or mineral acids to form the 1,2-disubstituted imidazoles **29** of the invention. Suitable solvents for this dehydration step are e.g., 10 toluene, xylene and benzene. Trifluoroacetic acid can be used as solvent and catalyst for this dehydration step.

In some cases (e.g., where YR = methyl or phenyl) the intermediate **28** may not be readily isolable. The 15 reaction, under the conditions described above, proceeds to give the targeted imidazoles directly.

Similarly, imidazoles can be prepared having the sulfonylphenyl moiety attached at position 2 and  $R^1$  attached at the nitrogen atom at position 1. 20 Diaryl/heteroaryl imidazoles can be prepared by the methods described in U.S. Patent Nos. 4,822,805, PCT document WO 96/03388 and PCT document WO 93/14082.

## Scheme VII

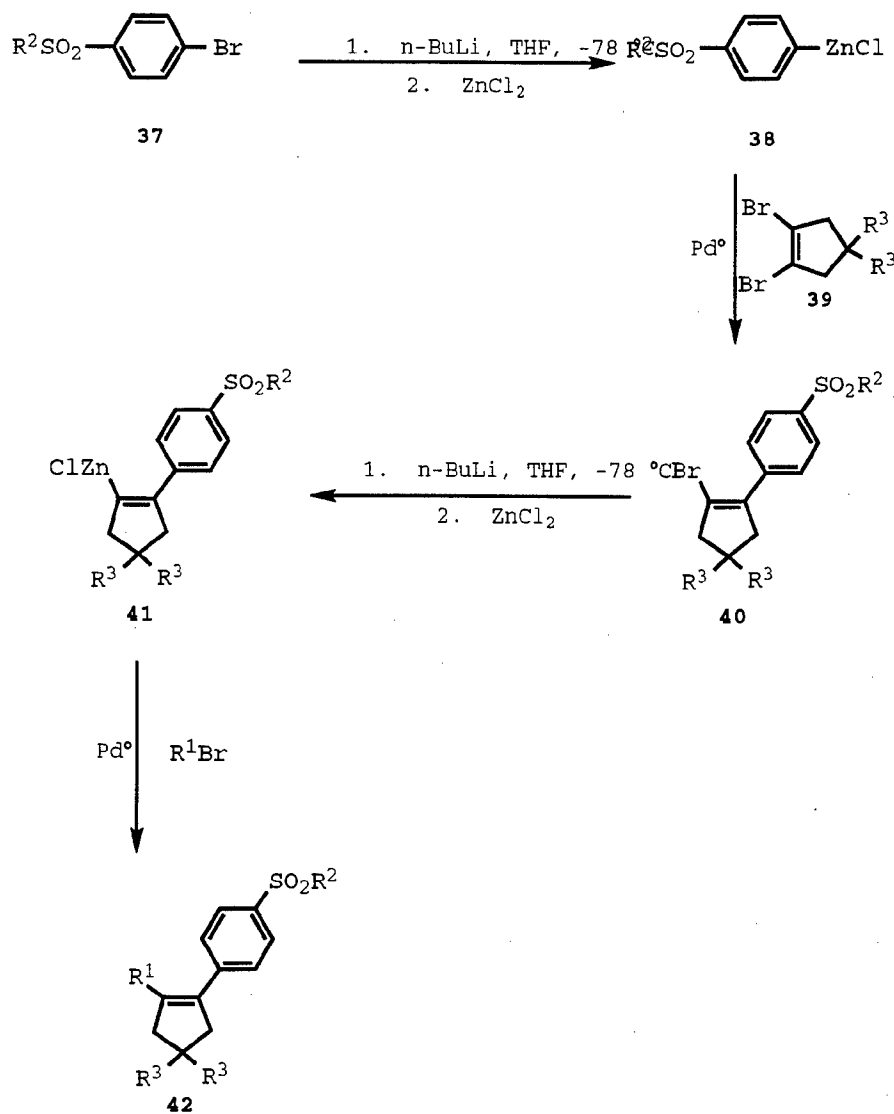


5        The subject imidazole cyclooxygenase-2 inhibitor  
 compounds 36 of this invention may be synthesized  
 according to the sequence outlined in Scheme VII.  
 Aldehyde 30 may be converted to the protected  
 cyanohydrin 31 by reaction with a trialkylsilyl  
 10    cyanide, such as trimethylsilyl cyanide (TMSCN) in the

presence of a catalyst such as zinc iodide ( $\text{ZnI}_2$ ) or potassium cyanide (KCN). Reaction of cyanohydrin **31** with a strong base followed by treatment with benzaldehyde **32** (where  $\text{R}^2$  is alkyl) and using both acid and base treatments, in that order, on workup gives benzoin **33**. Examples of strong bases suitable for this reaction are lithium diisopropylamide (LDA) and lithium hexamethyldisilazane. Benzoin **33** may be converted to benzil **34** by reaction with a suitable oxidizing agent, such as bismuth oxide or manganese dioxide, or by a Swern oxidation using dimethyl sulfoxide (DMSO) and trifluoroacetic anhydride. Benzil **34** may be obtained directly by reaction of the anion of cyanohydrin **31** with a substituted benzoic acid halide. Any of compounds **33** and **34** may be used as intermediates for conversion to imidazoles **35** (where  $\text{R}^2$  is alkyl) according to chemical procedures known by those skilled in the art and described by M. R. Grimmett, "Advances in Imidazole Chemistry" in **Advances in Heterocyclic Chemistry**, **12**, 104 (1970). The conversion of **34** to imidazoles **35** is carried out by reaction with ammonium acetate and an appropriate aldehyde ( $\text{RYCHO}$ ) in acetic acid. Benzoin **36** may be converted to imidazoles **38** by reaction with formamide. In addition, benzoin **36** may be converted to imidazoles by first acylating with an appropriate acyl group ( $\text{RYCO-}$ ) and then treating with ammonium hydroxide. Those skilled in the art will recognize that the oxidation of the sulfide (where  $\text{R}^2$  is methyl) to the sulfone may be carried out at any point along the way beginning with compounds **35**, and including oxidation of imidazoles **38**, using, for examples, reagents such as hydrogen peroxide in acetic acid, *m*-chloroperoxybenzoic acid (MCPBA) and potassium peroxymonosulfate (OXONE®).

Diaryl/heteroaryl imidazoles can be prepared by the methods described in U.S. Patent Nos. 3,707,475, 4,686,231, 4,503,065, 4,472,422, 4,372,964, 4,576,958, 3,901,908, PCT document WO 96/03387, 5 European publication EP 372,445, and PCT document WO 95/00501.

## Scheme VIII



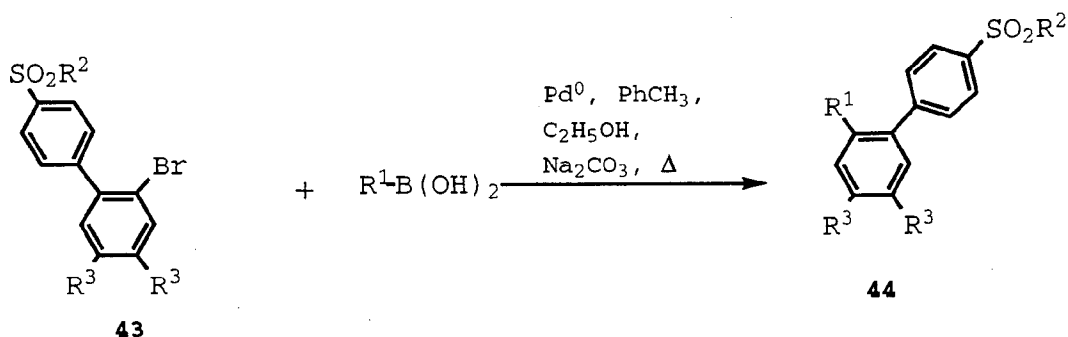
Diaryl/heteroaryl cyclopentene cyclooxygenase-2 inhibitors can be prepared by the methods described in



U.S. Patent No. 5,344,991, and PCT document WO 95/00501.

## Scheme IX

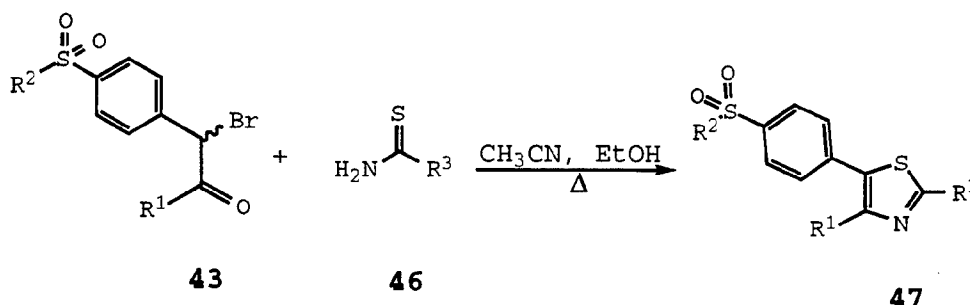
5



Similarly, Synthetic Scheme IX shows the procedure for the preparation of 1,2-diarylbenzene cyclooxygenase-2 inhibitor agents **44** from 2-bromobiphenyl intermediates **43** (prepared similar to that described in Synthetic Scheme VIII) and the appropriate substituted phenylboronic acids. Using a coupling procedure similar to the one developed by Suzuki et al. [*Synth. Commun.*, **11**, 513 (1981)], intermediates **43** are reacted with the boronic acids in toluene/ethanol at reflux in the presence of a  $Pd^0$  catalyst, e.g., tetrakis(triphenylphosphine)palladium(0), and 2M sodium carbonate to give the corresponding 1,2-diarylbenzene antiinflammatory agents **44** of this invention. Such terphenyl compounds can be prepared by the methods described by J. Li et al., [*J. Med. Chem.*, **39**, 1846-56 (1996)].

25

## Scheme X



Diaryl/heteroaryl thiazole cyclooxygenase-2

- 5 inhibitors can be prepared by the methods described in U.S. Patent No. 4,051,250, 4,632,930, PCT document WO 96/03392, European Application EP 592,664, and PCT document WO 95/00501. Isothiazoles can be prepared as described in PCT document WO 95/00501.
- 10 Aryl/heteroaryl substituted pyridine cyclooxygenase-2 inhibitors can be prepared by the methods described in U.S. Patent Nos. 5,169,857, 4,011,328, 4,533,666, and WO96/10012. Diaryl/heteroaryl benzofuran derivatives can be prepared by the methods described in
- 15 WO96/06840.

The following examples contain detailed descriptions of the methods of preparation of combinations with compounds of Formula I. These detailed descriptions fall within the scope, and serve

20 to exemplify, the above described General Synthetic Procedures which form part of the invention. These detailed descriptions are presented for illustrative purposes only and are not intended as a restriction on the scope of the invention. All parts are by weight

25 and temperatures are in Degrees centigrade unless otherwise indicated. All compounds showed NMR spectra consistent with their assigned structures.

## BIOLOGICAL EVALUATION

A combination therapy of a cyclooxygenase-2 inhibitor and a leukotriene B<sub>4</sub> receptor antagonist could be evaluated as described in the following tests.

## Example 1

4-[5-(4-Chlorophenyl)-3-(trifluoromethyl)-  
1H-pyrazol-1-yl]benzenesulfonamide

10

Step 1: Preparation of 4,4,4-trifluoro-1-[4-(chloro)phenyl]-butane-1,3-dione.

Ethyl trifluoroacetate (23.52 g, 166 mmol) was dissolved in methyl *tert*-butyl ether (75 mL). To the stirred solution was added 25 weight % sodium methoxide (40 mL, 177 mmol). Next 4'-chloroacetophenone (23.21 g, 150 mmol) was dissolved in methyl *tert*-butyl ether (20 mL), and added to the reaction dropwise. After stirring overnight (15.75 hours), 3N HCl (70 mL) was added. The organic layer was collected, washed with brine (75 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated in vacuo to give a 35.09 g of yellow-orange solid. The solid was recrystallized from isooctane to give 31.96 g (85%) of the dione: mp 66-67 °C.

Step 2: Preparation of 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide.

4-Sulphonamidophenyl hydrazine hydrochloride (982 mg, 4.4 mmol) was added to a stirred solution of 4,4,4-trifluoro-1-[4-(chloro)phenyl]-butane-1,3-dione (1.00 g, 4.0 mmol) in ethanol (50 mL). The reaction was heated to reflux and stirred for 20 hours. After cooling to room temperature, the reaction mixture was concentrated in vacuo. The residue was taken up in ethyl acetate and washed with water and brine and dried over MgSO<sub>4</sub>, filtered, and concentrated in vacuo to give a light brown solid which was recrystallized from ethyl acetate and isooctane to give the pyrazole (1.28 g, 80%): mp 143-145 °C. EI GC-MS M<sup>+</sup> = 401.

**Example 2**

4-[5-(3-Fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide

5 Step 1: Preparation of 3'-fluoro-4'-methoxy-acetophenone.

Acetyl chloride (51.0 g, 0.65 mol) was added dropwise to a stirred solution of aluminum chloride (80.0 g, 0.6 mol) and chloroform (750 mL), maintaining the temperature between 5-10°C. The mixture was stirred for 10 minutes at 5 °C before  
10 the dropwise addition of 2-fluoroanisole (62.6 g, 0.5 mol). The mixture was stirred at 0-10 °C for 1 hour and poured into ice (1 L). The resultant layers were separated and the aqueous layer was extracted with dichloromethane (2x250 mL). The combined organic layers were washed with water (2x150  
15 mL), dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated in vacuo to a volume of 300 mL. Hexanes were added and a white solid formed which was isolated by filtration and air dried. This material was recrystallized from a mixture of dichloromethane and hexanes to afford (77.2 g, 92%) of  
20 material suitable for use in the next step: mp 92-94 °C.

Step 2: Preparation of 4,4-difluoro-1-(3-fluoro-4-methoxyphenyl)-butane-1,3-dione.

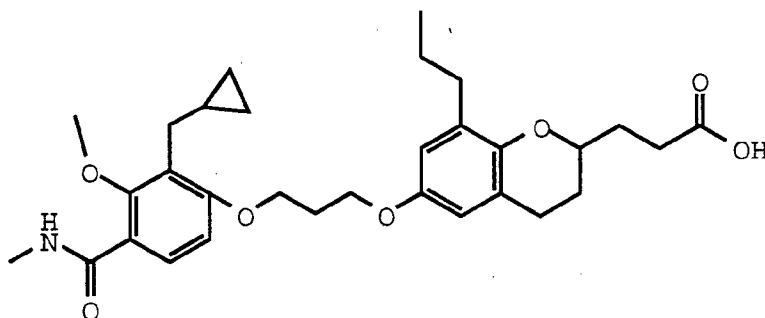
Ethyl difluoroacetate (4.06 g, 32.7 mmol) was dissolved  
25 in methyl t-butyl ether (50 mL). To the stirred solution was added 25 weight % sodium methoxide (7.07 g, 32.7 mmol) followed by 3'-fluoro-4'-methoxyacetophenone (5.0 g, 29.7 mmol). After stirring for 16 hours, 1N HCl (50 mL) was added. The organic layer was collected and washed with water (2x50  
30 mL), dried over anhydrous MgSO<sub>4</sub>, filtered, and added to hexanes to precipitate a tan solid (7.0 g, 96%): mp 70-72 °C.

Step 3: Preparation of 4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide.

35 4,4-Difluoro-1-(3-fluoro-4-methoxyphenyl)-butane-1,3-dione from Step 2 (7.0 g, 28.4 mmol) was dissolved in ethanol (150 mL). To the stirred mixture was added 4-sulphonamidophenyl hydrazine hydrochloride (7.4 g, 33 mmol)

and stirred at reflux overnight (16 hours). The mixture was cooled and water was added until crystals slowly appeared. The product was isolated by filtration and air dried to provide the desired product as a light tan solid (9.8 g, 87%): mp 159-161 °C. Anal. Calc'd. for C<sub>17</sub>H<sub>14</sub>N<sub>3</sub>SO<sub>3</sub>F<sub>3</sub>: C, 51.38; H, 3.55; N, 10.57. Found: C, 51.46; H, 3.52; N, 10.63.

### Example 3



7-[3-[2-(Cyclopropylmethyl)-3-methoxy-4-[(methylamino)carbonyl]phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-propanoic acid is prepared as in U.S. Patent No. 5,310,951, which is incorporated by reference.

### Induction and assessment of collagen induced arthritis in mice

Arthritis is induced in 8-12 week old male DBA/1 mice by injection of 50 µg of chick type II collagen (CII) (provided by Dr. Marie Griffiths, Univ. of Utah, Salt Lake City, UT) in complete Freund's adjuvant (Sigma) on day 0 at the base of the tail as previously described [J. Stuart, *Annual Rev. Immunol.*, **2**, 199 (1984)]. Compounds are prepared as a suspension in 0.5% methylcellulose (Sigma, St. Louis, MO), 0.025% Tween 20 (Sigma). The cyclooxygenase-2 inhibitors (Example 1 and 2) and leukotriene B<sub>4</sub> receptor antagonist (Example 3) are administered alone or a cyclooxygenase-2 inhibitor and a leukotriene B<sub>4</sub>

receptor antagonist in combination. The compounds are administered in non-arthritic animals by gavage in a volume of 0.1 ml beginning on day 20 post collagen injection and continuing daily until final evaluation on day 55. Animals are boosted on day 21 with 50 µg of collagen (CII) in incomplete Freund's adjuvant. The animals are subsequently evaluated several times each week for incidence and severity of arthritis until day 56. Any animal with paw redness or swelling is counted as arthritic. Scoring of severity is carried out using a score of 0-3 for each paw (maximal score of 12/mouse) as previously described [P. Wooley, et al., *Trans. Proc.*, **15**, 180 (1983)]. The animals are measured for incidence of arthritis and severity in the animals where arthritis is observed. The incidence of arthritis is determined at a gross level by observing the swelling or redness in the paw or digits. Severity is measured with the following guidelines. Briefly, animals displaying four normal paws, i.e., no redness or swelling are scored 0. Any redness or swelling of digits or the paw is scored as 1. Gross swelling of the whole paw or deformity is scored as 2. Ankylosis of joints is scored as 3.

#### **Histological Examination of Paws**

In order to verify the gross determination of a non-arthritic animal, a histological examination is performed. Paws from animals sacrificed at the end of the experiment are removed, fixed and decalcified as previously described [R. Jonsson, *J. Immunol. Methods*, **88**, 109 (1986)]. Samples are paraffin embedded, sectioned, and stained with hematoxylin and eosin by standard methods. Stained sections are examined for cellular infiltrates, synovial hyperplasia, and bone and cartilage erosion.

The animals are dosed at one of the following dosing ranges:

- a - Example 1 @ 3 mpk/day; Example 3 @ 3 mpk/day;
- 5 b - Example 2 @ 30 mpk/day; Example 3 @ 10 mpk/day;
- c - Example 2 @ 10 mpk/day; Example 3 @ 10 mpk/day;
- d - Example 1 M,W,F @ 10 mpk/day; Example 3 @ 10 mpk/day.

#### Example 4

10

A formulation is prepared having the following components:

700 mg of a cyclooxygenase-2 inhibitor and 700 mg of a leukotriene B<sub>4</sub> receptor antagonist.

15

#### Example 5

A formulation is prepared having the following components:

- 20 350 mg of 4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide and 350 mg of 7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-[(methylamino)carbonyl]phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-propanoic acid.

25

- Also embraced within this invention is a class of pharmaceutical compositions comprising the active compounds of this combination therapy in association with one or more non-toxic, pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The active compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The active compounds and composition may, for example, be administered orally, intravascularly, intraperitoneally, subcutaneously, intramuscularly or topically.

40

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier.

The amount of therapeutically active compounds that are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the disease, the route and frequency of administration, and the particular compound employed, and thus may vary widely. The pharmaceutical compositions may contain active ingredients in the range of about 0.1 to 2000 mg, preferably in the range of about 0.5 to 500 mg and most preferably between about 1 and 100 mg. A daily dose of about 0.01 to 100 mg/kg body weight, preferably between about 0.5 and about 20 mg/kg body weight and most preferably between about 0.1 to 10 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day.

In the case of psoriasis and other skin conditions, it may be preferable to apply a topical preparation of compounds of this invention to the affected area two to four times a day.

For inflammations of the eye or other external tissues, e.g., mouth and skin, the formulations are preferably applied as a topical ointment or cream, or as a suppository, containing the active ingredients in a total amount of, for example, 0.075 to 30% w/w, preferably 0.2 to 20% w/w and most preferably 0.4 to 15% w/w. When formulated in an ointment, the active



ingredients may be employed with either paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example at least 30% w/w of a polyhydric alcohol such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogs. The compounds of this invention can also be administered by a transdermal device. Preferably topical administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered continuously from the reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and

fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, and sodium lauryl sulfate, among others.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus, the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters may be used. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredients are dissolved or suspended in suitable carrier, especially an aqueous solvent for the active ingredients. The antiinflammatory active ingredients are preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% and particularly about 1.5% w/w.

For therapeutic purposes, the active compounds of this combination invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered *per os*, the compounds may be admixed with lactose,

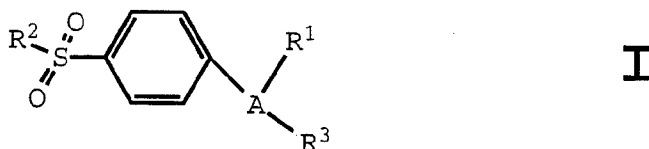
sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, 5 gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a 10 dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile 15 powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame 20 oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Although this invention has been described with respect to specific embodiments, the details of these 25 embodiments are not to be construed as limitations.

What is claimed is :

1. A combination comprising a therapeutically-effective amount of a cyclooxygenase-2 inhibitor and a  
5 leukotriene B<sub>4</sub> receptor antagonist.

2. A combination comprising a therapeutically-effective amount of a leukotriene B<sub>4</sub> receptor antagonist and a cyclooxygenase-2 inhibitor selected from Taisho  
10 NS-398, meloxicam, floculide, Merck MK-966, Merck L-752,860 and compounds of Formula I



15 wherein A is a substituent selected from partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

wherein R<sup>1</sup> is at least one substituent selected from heterocyclyl, cycloalkyl, cycloalkenyl and aryl,  
20 wherein R<sup>1</sup> is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and  
25 alkylthio;

wherein R<sup>2</sup> is methyl or amino; and

wherein R<sup>3</sup> is a radical selected from hydrido, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocycliloxy, alkyloxy, alkylthio,  
30 alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl,  
35 aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl,

aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl,  
N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl,  
alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-  
arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-  
5 alkyl-N-arylmino, aminoalkyl, alkylaminoalkyl, N-  
arylminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-  
aralkylaminoalkyl, N-alkyl-N-arylminoalkyl, aryloxy,  
aralkoxy, arylthio, aralkylthio, alkylsulfinyl,  
alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-  
10 arylaminosulfonyl, arylsulfonyl, N-alkyl-N-  
arylaminosulfonyl;

or a pharmaceutically-acceptable salt thereof.

3. The combination of Claim 2 wherein the  
15 leukotriene B<sub>4</sub> receptor antagonist is selected from  
Bayer Bay-x-1005, Ciba-Geigy CGS-25019C, ebselen, Leo  
Denmark ETH-615, Lilly LY-293111, Ono ONO-4057, Terumo  
TMK-688, Boehringer Ingleheim BI-RM-270, Lilly LY  
213024, Lilly LY 264086, Lilly LY 292728, Ono ONO  
20 LB457, Pfizer 105696, Perdue Frederick PF 10042, Rhone-  
Poulenc Rorer RP 66153, SmithKline Beecham SB-201146,  
SmithKline Beecham SB-201993, Searle SC-53228, Sumitamo  
SM 15178, American Home Products WAY 121006, Bayer Bay-  
o-8276, calcitriol, Warner-Lambert CI-987, Merck and  
25 Co. L-651392, Lilly LY 210073, Lilly LY 223982, Lilly  
LY 233569, Lilly LY-255283, Merck and Co. MK-591, Merck  
and CO. MK-886, Ono ONO-LB-448, Purdue Frederick PF-  
5901, Rhone-Poulenc Rorer RG 14893, Rhone-Poulenc Rorer  
RP 66364, Rhone-Poulenc Rorer RP 69698, Searle SC-  
30 41930, Searle SC-50505, Searle SC-51146, SmithKline  
Beecham SK&F-104493, and Teijin TEI-1338.

4. The combination of Claim 3 wherein the  
leukotriene B<sub>4</sub> receptor antagonist is selected from  
35 Bayer Bay-x-1005, Ciba-Geigy CGS-25019C, ebselen, Leo  
Denmark ETH-615, Lilly LY-293111, Ono ONO-4057, Terumo  
TMK-688, Boehringer Ingleheim BI-RM-270, Lilly LY

213024, Lilly LY 264086, Lilly LY 292728, Ono ONO LB457, Pfizer 105696, Perdue Frederick PF 10042, Rhone-Poulenc Rorer RP 66153, SmithKline Beecham SB-201146, SmithKline Beecham SB-201993, Searle SC-53228, Sumitamo SM 15178, and American Home Products WAY 121006.

5. The combination of Claim 4 wherein the leukotriene B<sub>4</sub> receptor antagonist is selected from Bayer Bay-x-1005, Ciba-Geigy CGS-25019C, ebselen, Leo Denmark ETH-615, Lilly LY-293111, Ono ONO-4057, and Terumo TMK-688.

6. The combination of Claim 2 wherein A is selected from 5- or 6-member partially unsaturated heterocyclyl, 5- or 6-member unsaturated heterocyclyl, 9- or 10-member unsaturated condensed heterocyclyl, lower cycloalkenyl and phenyl; wherein R<sup>1</sup> is selected from 5- and 6-membered heterocyclyl, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R<sup>1</sup> is optionally substituted at a substitutable position with one or more radicals selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxy carbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylamino, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio; wherein R<sup>2</sup> is methyl or amino; and wherein R<sup>3</sup> is a radical selected from hydrido, oxo, cyano, carboxyl, lower alkoxy carbonyl, lower carboxyalkyl, lower cyanoalkyl, halo, lower alkyl, lower alkyloxy, lower cycloalkyl, phenyl, lower haloalkyl, 5- or 6-membered heterocyclyl, lower hydroxyalkyl, lower aralkyl, acyl, phenylcarbonyl, lower alkoxyalkyl, 5- or 6-membered heteroaryloxy, aminocarbonyl, lower alkylaminocarbonyl, lower alkylamino, lower aminoalkyl, lower alkylaminoalkyl, phenyloxy, and lower aralkoxy; or a pharmaceutically-acceptable salt thereof.

7. The combination of Claim 6 wherein A is selected from oxazolyl, isoxazolyl, thienyl, dihydrofuryl, furyl, pyrrolyl, pyrazolyl, thiazolyl, imidazolyl, isothiazolyl, benzofuryl, cyclopentenyl, cyclopentadienyl, phenyl, and pyridyl; wherein R<sup>1</sup> is selected from pyridyl optionally substituted at a substitutable position with one or more methyl radicals, and phenyl optionally substituted at a substitutable position with one or more radicals selected from methyl, ethyl, isopropyl, butyl, *tert*-butyl, isobutyl, pentyl, hexyl, cyano, fluoromethyl, difluoromethyl, trifluoromethyl, carboxyl, methoxycarbonyl, ethoxycarbonyl, hydroxymethyl, trifluoromethoxy, hydroxyl, amino, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-dipropylamino, N-butylamino, N-methyl-N-ethylamino, phenylamino, methoxymethyl, methylsulfinyl, fluoro, chloro, bromo, methoxy, ethoxy, propoxy, *n*-butoxy, pentoxy, and methylthio; wherein R<sup>2</sup> is methyl or amino; and wherein R<sup>3</sup> is a radical selected from hydrido, oxo, cyano, carboxyl, methoxycarbonyl, ethoxycarbonyl, carboxypropyl, carboxymethyl, carboxyethyl, cyanomethyl, fluoro, chloro, bromo, methyl, ethyl, isopropyl, butyl, *tert*-butyl, isobutyl, pentyl, hexyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, heptafluoropropyl, difluoroethyl, difluoropropyl, methoxy, ethoxy, propoxy, *n*-butoxy, pentoxy, cyclohexyl, phenyl, pyridyl, thienyl, thiazolyl, oxazolyl, furyl, pyrazinyl, hydroxylmethyl, hydroxylpropyl, benzyl, formyl, phenylcarbonyl, methoxymethyl, furylmethyloxy, aminocarbonyl, N-methylaminocarbonyl, N,N-dimethylaminocarbonyl, N,N-dimethylamino, N-ethylamino, N,N-dipropylamino, N-butylamino, N-methyl-N-ethylamino, aminomethyl, N,N-dimethylaminomethyl, N-methyl-N-ethylaminomethyl,

benzyloxy, and phenyloxy; or a pharmaceutically-acceptable salt thereof.

8. The combination of Claim 7 selected from  
5 compounds, their prodrugs and their pharmaceutically-acceptable salts, of the group consisting of

- 5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole;  
10 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)pyrazole;  
4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide  
4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;  
15 4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide;  
4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;  
20 4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;  
4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl)benzenesulfonamide;  
4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-yl)benzenesulfonamide;  
25 4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-yl)benzenesulfonamide  
4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;  
30 4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;  
4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;  
4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;  
35 4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;



- 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 5 4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;
- 4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 10 4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 15 4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;
- 4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 20 4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
- 4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
- 25 6-(4-fluorophenyl)-7-[4-(methylsulfonyl)phenyl]spiro[3.4]oct-6-ene;
- 5-(3-chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
- 30 4-[6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
- 5-(3,5-dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
- 5-(3-chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
- 35 4-[6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;

- 2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;
- 2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;
- 5 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole;
- 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;
- 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole;
- 10 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole;
- 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole;
- 15 2-[(3,5-dichlorophenoxy)methyl]-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]thiazole;
- 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;
- 1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene;
- 20 4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl]benzenesulfonamide;
- 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hepta-4,6-diene;
- 25 4-[6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-yl]benzenesulfonamide;
- 6-(4-fluorophenyl)-2-methoxy-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;
- 2-bromo-6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;
- 30 6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenylpyridine-3-carbonitrile;
- 4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 35 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

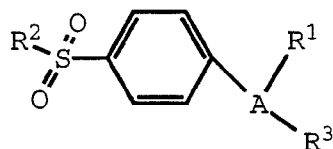
- 4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
- 5 2-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
- 2-methyl-4-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
- 2-methyl-6-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
- 10 4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
- 15 4-[2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-methyl-1H-imidazole;
- 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-1H-imidazole;
- 20 2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 2-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
- 25 1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole;
- 2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
- 4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 30 2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
- 4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 35 2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;

- 4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- 1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole;
- 5 4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- 10 1-allyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;
- 4-[1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl]benzenesulfonamide;
- 15 N-phenyl-[4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;
- ethyl [4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetate;
- 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-1H-pyrazole;
- 20 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole;
- 1-ethyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;
- 25 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethyl-1H-imidazole;
- 4-[4-(methylsulfonyl)phenyl]-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole;
- 5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;
- 30 2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;
- 5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-(2-propynyloxy)-6-(trifluoromethyl)pyridine;
- 35 2-bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

- 4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide;  
1-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
5-difluoromethyl-4-(4-methylsulfonylphenyl)-3-phenylisoxazole;  
5 4-[3-ethyl-5-phenylisoxazol-4-yl]benzenesulfonamide;  
4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;  
4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;  
10 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;  
1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;  
1-[2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;  
15 1-[2-(4-chlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;  
1-[2-(2,4-dichlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;  
20 1-[2-(4-trifluoromethylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;  
1-[2-(4-methylthiophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;  
1-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;  
25 4-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;  
1-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;  
30 4-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;  
4-[2-(4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;  
4-[2-(4-chlorophenyl)cyclopenten-1-yl]benzenesulfonamide;  
1-[2-(4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;  
35 1-[2-(2,3-difluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

- 4-[2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-yl]benzenesulfonamide;  
 1-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;  
 5 4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;  
 4-[2-(2-methylpyridin-5-yl)cyclopenten-1-yl]benzenesulfonamide;  
 ethyl 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]-2-benzyl-acetate;  
 10 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]acetic acid;  
 2-(tert-butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole;  
 15 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole;  
 4-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole; and  
 4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide.

9. A pharmaceutical composition comprising a pharmaceutically-acceptable carrier and a therapeutically-effective amount of a leukotriene B<sub>4</sub>  
 25 receptor antagonist and a cyclooxygenase-2 inhibitor selected from Taisho NS-398, meloxicam, floculide, Merck MK-966, Merck L-752,860 and compounds of Formula I



I

30

wherein A is a substituent selected from partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

wherein R<sup>1</sup> is at least one substituent selected from heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R<sup>1</sup> is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

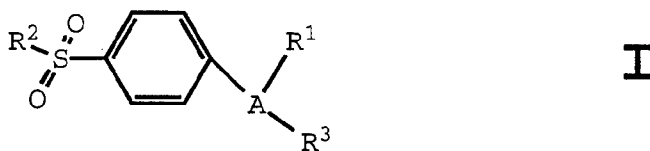
wherein R<sup>2</sup> is methyl or amino; and

wherein R<sup>3</sup> is a radical selected from hydrido, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminalkyl, N-aralkylaminalkyl, N-alkyl-N-aralkylaminalkyl, N-alkyl-N-arylaminalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N-alkyl-N-arylaminosulfonyl;

or a pharmaceutically-acceptable salt thereof.

10. A method of treating inflammation or an inflammation-associated disorder in a subject, said method comprising co-administering to the subject having or susceptible to such inflammation or inflammation-associated disorder, a therapeutically-effective amount of a leukotriene B<sub>4</sub> receptor antagonist and a

cyclooxygenase-2 inhibitor selected from Taisho NS-398, meloxicam, floculide, Merck MK-966, Merck L-752,860 and compounds of Formula I



5

wherein A is a substituent selected from partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

10        wherein R<sup>1</sup> is at least one substituent selected from heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R<sup>1</sup> is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

         wherein R<sup>2</sup> is methyl or amino; and

         wherein R<sup>3</sup> is a radical selected from hydrido, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocycliloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminalkyl, N-aralkylaminalkyl, N-alkyl-N-aralkylaminalkyl, N-alkyl-N-arylaminalkyl, aryloxy,

20  
25  
30



aralkoxy, arylthio, aralkylthio, alkylsulfinyl,  
alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-  
arylamino sulfonyl, arylsulfonyl, N-alkyl-N-  
arylamino sulfonyl;

5 or a pharmaceutically-acceptable salt thereof.

11. The method of Claim 10 wherein said leukotriene B<sub>4</sub>  
receptor antagonist and said cyclooxygenase-2 inhibitor are  
administered in a sequential manner.

10

12. The method of Claim 10 wherein said leukotriene B<sub>4</sub>  
receptor antagonist and said cyclooxygenase-2 inhibitor are  
administered in a substantially simultaneous manner.

15 13. The method of Claim 10 wherein the leukotriene  
B<sub>4</sub> receptor antagonist is selected from compounds of  
Claim 4.

14. The method of Claim 13 wherein the leukotriene  
20 B<sub>4</sub> receptor antagonist is selected from compounds of  
Claim 5.

15. The method of Claim 10 wherein the  
cyclooxygenase-2 inhibitor is selected compounds of  
25 Claim 6, or a pharmaceutically-acceptable salt thereof.

16. The method of Claim 15 wherein the  
cyclooxygenase-2 inhibitor is selected compounds of  
Claim 7, or a pharmaceutically-acceptable salt thereof.

30

17. The method of Claim 16 wherein the  
cyclooxygenase-2 inhibitor is selected compounds of  
Claim 8, or a pharmaceutically-acceptable salt thereof.

35 18. The method of Claim 10 wherein the condition is  
inflammation.

19. The method of Claim 10 wherein the condition is an inflammation-associated disorder.

20. The method of Claim 19 wherein the  
5 inflammation-associated disorder is arthritis.

21. The method of Claim 10 wherein the subject is susceptible to inflammation.

10 22. The method of Claim 10 wherein the subject is susceptible to an inflammation-associated disorder.

23. The method of Claim 22 wherein the subject is susceptible to arthritis.

15

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 96/09905

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K45/06

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE,A,42 28 201 (SCHERING AG) 3 March 1994 see page 6, line 55 - line 59 ---	1
X,P	WO,A,96 03385 (SEARLE & CO ; LEE LEN F (US); PENNING THOMAS D (US); KRAMER STEVEN) 8 February 1996 see page 5, paragraph 3-4 ---	1-23
X,P	WO,A,96 03388 (SEARLE & CO ; KHANNA ISH K (US); WEIER RICHARD M (US); COLLINS PAUL) 8 February 1996 cited in the application see page 6, line 1 - line 19 see abstract --- -/--	1-23

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

27 November 1996

Date of mailing of the international search report

0 5. 12. 96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax (+31-70) 340-3016

Authorized officer

Leherte, C

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 96/09905

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO,A,96 03387 (SEARLE & CO ;WEIER RICHARD M (US); COLLINS PAUL W (US); STEALEY MI) 8 February 1996 cited in the application see page 8, line 2-21 see abstract	1-23
P,Y	--- US,A,5 510 368 (LAU CHEUK K ET AL) 23 April 1996 cited in the application see abstract	1-23
Y	--- WO,A,95 15316 (SEARLE & CO ;TALLEY JOHN J (US); PENNING THOMAS D (US); COLLINS PA) 8 June 1995 cited in the application see abstract	1-23
Y	--- WO,A,94 26731 (MERCK FROSST CANADA INC ;GAUTHIER JACQUES YVES (CA); LEBLANC YVES) 24 November 1994 cited in the application see abstract	1-23
Y	--- WO,A,95 00501 (MERCK FROSST CANADA INC ;DUCHARME YVES (CA); GAUTHIER JACQUES YVES) 5 January 1995 cited in the application see abstract see page 26, line 1-21	1-23
Y	--- WO,A,94 20480 (MERCK FROSST CANADA INC ;BLACK CAMERON W (CA); GUAY DANIEL (CA); L) 15 September 1994 cited in the application see abstract	1-23
Y	--- WO,A,94 13635 (MERCK FROSST CANADA INC ;FORD HUTCHINSON ANTHONY W (CA); KENNEDY B) 23 June 1994 cited in the application see abstract	1-23
Y	--- WO,A,94 15932 (SEARLE & CO ;MONSANTO CO (US); BERTENSHAW STEPHEN R (US); COLLINS) 21 July 1994 cited in the application see abstract	1-23
Y	--- US,A,5 246 965 (MAIN ALAN J) 21 September 1993 cited in the application see abstract	1-23
	--- -/--	

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 96/09905

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US,A,5 384 318 (EGGLER JAMES F ET AL) 24 January 1995 cited in the application see abstract	1-23
Y	--- WO,A,94 27980 (SEARLE & CO ;NORMAN BRYAN H (US); LEE LEN F (US); MASFERRER JAIME) 8 December 1994 cited in the application see abstract	1-23
Y	--- US,A,5 344 991 (REITZ DAVID B ET AL) 6 September 1994 cited in the application see abstract	1-23
Y	--- US,A,5 393 790 (REITZ DAVID B ET AL) 28 February 1995 cited in the application see abstract -----	1-23

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 96/09905

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claim(s) 10-23  
is(are) directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compound/composition.
2. ☒ Claims Nos.: 1-23  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:  
In view of the large number of compounds which are defined by the wording  
of the claims, the search has been performed on the general idea and  
compounds mentioned in the examples of the description.
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/09905

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE-A-4228201	03-03-94	AU-A- 4950593	15-03-94
		CA-A- 2142821	03-03-94
		WO-A- 9404522	03-03-94
		EP-A- 0656896	14-06-95
		HU-A- 70511	30-10-95
		JP-T- 8500585	23-01-96
		NO-A- 950708	24-02-95
		US-A- 5559134	24-09-96
-----			
WO-A-9603385	08-02-96	US-A- 5486534	23-01-96
		AU-A- 3126795	22-02-96
-----			
WO-A-9603388	08-02-96	AU-A- 3202595	22-02-96
-----			
WO-A-9603387	08-02-96	AU-A- 3271695	22-02-96
-----			
US-A-5510368	23-04-96	NONE	
-----			
WO-A-9515316	08-06-95	US-A- 5466823	14-11-95
		US-A- 5521207	28-05-96
		AU-A- 1171495	19-06-95
		CA-A- 2177576	08-06-95
		EP-A- 0731795	18-09-96
		FI-A- 962249	29-05-96
		NO-A- 962184	29-05-96
		PL-A- 314695	16-09-96
		US-A- 5510496	23-04-96
		US-A- 5563165	08-10-96
		US-A- 5508426	16-04-96
		US-A- 5516907	14-05-96
		US-A- 5504215	02-04-96
		ZA-A- 9409418	28-11-95
-----			
WO-A-9426731	24-11-94	AU-A- 6718494	12-12-94
-----			
WO-A-9500501	05-01-95	US-A- 5474995	12-12-95
		AU-A- 6197096	31-10-96
		AU-A- 6967494	17-01-95
		BG-A- 100247	28-06-96
		BR-A- 9406979	05-03-96

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/09905

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9500501		CA-A- 2163888	05-01-95
		CA-A- 2176973	25-12-94
		CA-A- 2176974	25-12-94
		CN-A- 1125944	03-07-96
		CZ-A- 9503146	15-05-96
		EP-A- 0705254	10-04-96
		FI-A- 956119	19-12-95
		NO-A- 955256	23-02-96
		PL-A- 312196	01-04-96
		US-A- 5536752	16-07-96
		US-A- 5550142	27-08-96
		ZA-A- 9404501	13-03-95
		AU-A- 1269495	01-08-95
		CA-A- 2180651	13-07-95
		WO-A- 9518799	13-07-95
		EP-A- 0739340	30-10-96
		FI-A- 962800	06-09-96
		NO-A- 960393	09-07-96
-----			
WO-A-9420480	15-09-94	US-A- 5409944	25-04-95
		AU-A- 6178894	26-09-94
		CA-A- 2157107	14-09-94
-----			
WO-A-9413635	23-06-94	AU-A- 5621594	04-07-94
		CA-A- 2151235	23-06-94
		EP-A- 0673366	27-09-95
		JP-T- 8504408	14-05-96
-----			
WO-A-9415932	21-07-94	AU-A- 6027694	15-08-94
		CA-A- 2152792	21-07-94
		EP-A- 0679157	02-11-95
-----			
US-A-5246965	21-09-93	AU-A- 1807292	17-12-92
		CA-A- 2070796	12-12-92
		EP-A- 0518818	16-12-92
		HU-A- 61977	29-03-93
		JP-A- 5239008	17-09-93
-----			
US-A-5384318	24-01-95	WO-A- 9015801	27-12-90
		CA-A- 2019349	22-12-90



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/09905

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-5384318		EP-A- 0404440	27-12-90
		FI-B- 96951	14-06-96
		JP-A- 3038569	19-02-91
		JP-B- 7053722	07-06-95
-----			
WO-A-9427980	08-12-94	US-A- 5380738	10-01-95
		AU-A- 6949594	20-12-94
		EP-A- 0699192	06-03-96
-----			
US-A-5344991	06-09-94	AU-A- 7365094	22-05-95
		CA-A- 2170736	04-05-95
		EP-A- 0724566	07-08-96
		WO-A- 9511883	04-05-95
		US-A- 5420287	30-05-95
-----			
US-A-5393790	28-02-95	AU-A- 1740895	29-08-95
		CA-A- 2182950	17-08-95
		EP-A- 0743938	27-11-96
		WO-A- 9521817	17-08-95
		ZA-A- 9501107	12-02-96
-----			